

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
LUBISCH et al.) Applications

Serial No. Not Assigned)
)
Filed:)
)

For: DIBENZODIAZEPINE DERIVATIVES, THEIR PREPARATION AND USE

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown in the attached sheets.

R E M A R K S

The claims have been amended to eliminate multiple dependency. No new matter has been added. A clean copy of the claims is attached.

Entry of the above amendment is respectfully solicited.

Respectfully submitted,

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CLEAN VERSION OF AMENDED CLAIMS - 33827-US-009

2. Compounds of the formula I according to claim 1, in which
 - A denotes a benzo ring,
 - X¹ denotes O, and
 - R¹ denotes hydrogen.
3. Compounds of the formula I according to claim 1, in which
 - B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R⁴ or at most 2 R⁵.
4. Compounds of the formula I according to claim 1, in which
 - L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R⁴ radicals and at most two different or identical R⁵ radicals,
 - v denotes 1, and
 - w denotes 0 or 1.
5. Compounds of the formula I according to claim 1, in which
 - R⁴ denotes D_{0,1}-F¹_{0,1}-G²-G³, where G³ denotes hydrogen,
 - D denotes O or NR⁴³, where R⁴³ denotes hydrogen or C₁-C₃-alkyl, and
 - F¹ denotes C₂-C₄-alkyl.
6. Compounds of the formula I according to claim 1, in which

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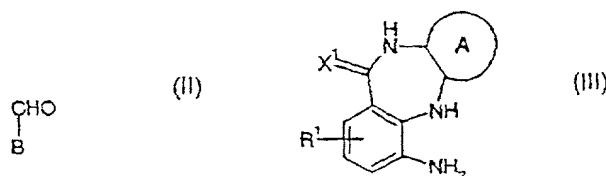
R^4 denotes $G^1-F^1_0,-G^2-G^3$, where G^3 denotes hydrogen, and
 F^1 denotes C_1-C_2 -alkyl.

7. Compounds of the formula I according to claim 6, in which
 - G^1 denotes imidazole or pyrrole, where the pyrrole can in each case be substituted by at most three different or identical R^5 radicals, and
 - F^1 denotes C_1-C_2 -alkyl.
8. Pharmaceutical composition which comprises at least one compound according to claim 1 and also at least one customary carrier and/or auxiliary substance.
9. Use of a compound of formula I according to claim 1 for producing a pharmaceutical for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections.
10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial

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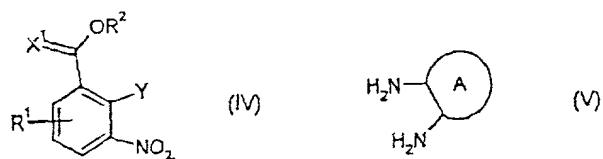
infraction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at least one compound of the formula I according to claim 1.

11. Process for producing a compound according to claim 1, which comprises condensing an aldehyde of the formula II with a diamine of the formula III:



where the symbols in the formulae II and III have the same meaning as in claim 1.

12. Process according to claim 11, where the diamine of the formula III is obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



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where the symbols in the formulae IV and V have the same meaning as in
Claim 1 and R² denotes branched or unbranched, saturated or
unsaturated C₁-C₆-alkyl.

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2. Compounds of the formula I according to [Claim] claim 1, in which

A denotes a benzo ring,

X¹ denotes O, and

R¹ denotes hydrogen.

3. Compounds of the formula I according to claim 1 [Claim 1 or 2], in which

B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R⁴ or at most 2 R⁵.

4. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 3], in which

L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R⁴ radicals and at most two different or identical R⁵ radicals,

v denotes 1, and

w denotes 0 or 1.

5. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 4], in which

R⁴ denotes D_{0,1}-F¹_{0,1}-G²-G³, where G³ denotes hydrogen,

D denotes O or NR⁴³, where R⁴³ denotes hydrogen or C₁-C₃-alkyl, and

F¹ denotes C₂-C₄-alkyl.

6. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 4],

in which

R⁴ denotes G¹-F¹, -G²-G³, where G³ denotes hydrogen, and

F¹ denotes C₁-C₂-alkyl.

7. Compounds of the formula I according to [Claim] claim 6, in which

G¹ denotes imidazole or pyrrole, where the pyrrole can in each case be substituted by at most three different or identical R⁵ radicals, and

F¹ denotes C₁-C₂-alkyl.

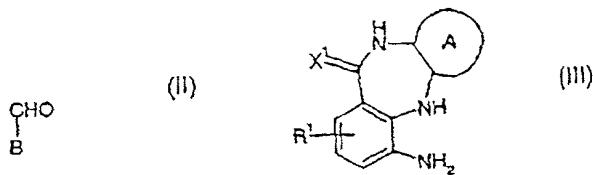
8. Pharmaceutical composition which comprises at least one compound according to claim 1 [one of Claims 1 to 7] and also at least one customary carrier and/or auxiliary substance.

9. Use of a compound of formula I according to claim 1 [one of Claims 1 to 7] for producing a pharmaceutical for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections.

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10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at least one compound of the formula I according to claim 1 [one of Claims 1 to 7].

11. Process for producing a compound according to claim 1 [one of Claims 1 to 7], which comprises condensing an aldehyde of the formula II with a diamine of the formula III:

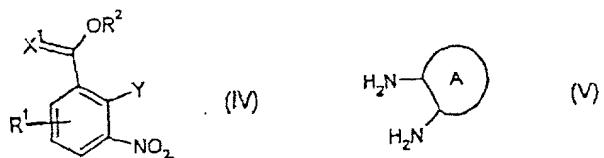


where the symbols in the formulae II and III have the same meaning as in claim [Claim] 1.

12. Process according to claim [Claim] 11, where the diamine of the formula III is

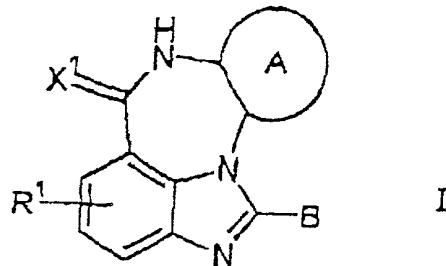
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obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



where the symbols in the formulae IV and V have the same meaning as in Claim 1 and R² denotes branched or unbranched, saturated or unsaturated C₁-C₆-alkyl.

1. Compounds of the formula I



in which

A denotes a saturated, unsaturated or partially unsaturated ring having at most 6 carbon atoms or an unsaturated or partially unsaturated ring having at most 5 carbon atoms and from 1 to 3 nitrogen atoms, one oxygen atom and/or one sulphur atom,

X¹ denotes S, O and NH, and

R¹ denotes hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C₁-C₆-alkyl, OH, nitro, CF₃, CN, NR¹¹ R¹², NH-CO-R¹³, or O-C₁-C₄-alkyl, where R¹¹ and R¹², independently of each other, denote hydrogen or C₁-C₄-alkyl, and R¹³ denotes hydrogen, C₁-C₄-alkyl, C₁-C₄-alkylphenyl or phenyl,

B denotes an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, where the respective ring can be additionally substituted by one R⁴ and at most 3 different or identical R⁵ radicals, and one or two carbon, or sulphur,

atoms can also carry one or two $=\text{O}$ groups, such as keto groups, sulphones or sulphoxides, or denotes a radical $\text{L}_v\text{-Y-}\text{M}_w$, in which

L denotes a straight-chain or branched saturated or unsaturated carbon chain of from 1 to 8 C atoms, where each carbon atom can be substituted by one or two R^4 radicals and at most two different or identical R^5 radicals,

M possesses, independently of L, the same meaning as L, and

Y denotes a bond, S, O or NR^3 , where R^3 is hydrogen, branched or unbranched $\text{C}_1\text{-C}_6$ -alkyl, $\text{C}_1\text{-C}_4$ -alkylphenyl or phenyl, and

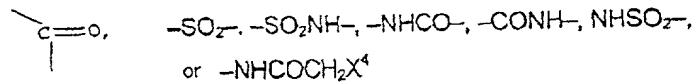
v denotes 0 and 1, and

w denotes 0 and 1,

R^4 denotes hydrogen or $-(\text{D})_p-(\text{E})_s-(\text{F}^1)_q-\text{G}^1-(\text{F}^2)_r-\text{G}^2-\text{G}^3$, where

D denotes S, NR^{43} or O,

E denotes phenyl,



X^4 denotes S, O or NH,

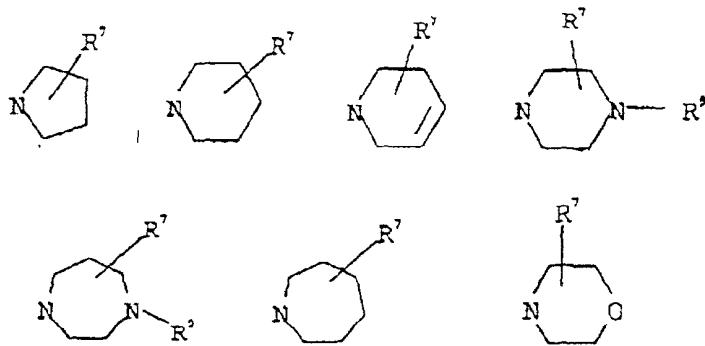
F^1 denotes a straight-chain or branched, saturated or unsaturated carbon chain of from 1 to 8 C atoms,

F^2 independently of F_1 possesses the same meaning as F_1 ,

G^1 denotes a bond, an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or

partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, where the respective ring can be additionally substituted by at most 3 different or identical R⁵ radicals, and one or two carbon and/or sulphur atoms can also carry one or two =O groups, and

G² denotes NR⁴¹R⁴²,



or a bond,

G³ denotes an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms where the respective ring additionally substituted by at most 3 different or identical R⁵ radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups, or denotes hydrogen,

p denotes 0 or 1,

s denotes 0 or 1,

q denotes 0 or 1,

r denotes 0 or 1,

R^{41} denotes hydrogen, C_1 - C_6 -alkyl, where each carbon atom can additionally carry up to 2 R^6 radicals, phenyl, which can additionally carry at most 2 R^6 radicals, and $(CH_2)_t$ -K, and

R^{42} denotes hydrogen, C_1 - C_6 -alkyl, $-CO-R^8$, SO_2NH_2 , SO_2-R^8 , $-(C=NH)-R^8$ and $(C=NH)-NHR^8$,

R^{43} denotes hydrogen and C_1 - C_4 -alkyl,

t denotes 1, 2, 3 or 4,

K denotes $NR^{11}R^{12}$, $NR^{11}-C_1$ - C_4 -alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, homopiperidine, piperazine, which can be additionally substituted by an alkyl radical C_1 - C_6 -alkyl, and homopiperazine, which can be additionally substituted by an alkyl radical C_1 - C_6 -alkyl,

R^5 denotes hydrogen, chlorine, fluorine, bromine, iodine, OH, nitro, CF_3 , CN, $NR^{11}R^{12}$, $NH-CO-R^{13}$, C_1 - C_4 -alkyl $-CO-H-R^{13}$, COR^8 , C_0 - C_4 -alkyl-O-CO- R^{13} , C_1 - C_4 -alkylphenyl, phenyl, CO_2-C_1 - C_4 -alkyl and branched and unbranched C_1 - C_6 -alkyl, O- C_1 - C_4 -alkyl or S- C_1 - C_4 -alkyl where each C atom of the alkyl chains can carry up to two R^6 chains can be unsaturated, radicals and the alkyl chains can be unsaturated

R^6 denotes hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C_1 - C_6 -alkyl, OH, nitro, CF_3 , CN, $NR^{11}R^{12}$, $NH-CO-R^{13}$ or O- C_1 - C_4 -alkyl,

R^7 denotes hydrogen, C_1 - C_6 -alkyl, phenyl, where the phenyl ring can be additionally

substituted by up to two R⁷¹ radicals, and an amine NR¹¹R¹² or a cyclic saturated amine having from 3 to 7 members which can additionally be substituted by an alkyl radical C₁-C₆-alkyl, and homopiperazine which can be additionally substituted by an alkyl radical C₁-C₆-alkyl,

where the radicals R¹¹, R¹² and R¹³ in K, R⁵, R⁶, and R⁷ can, independently of each other, assume meaning as R¹,

R⁷¹ denotes OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro or NH₂,

R⁸ denotes C₁-C₆-alkyl, CF₃, phenyl or C₁-C₄-alkylphenyl, where the ring can additionally be substituted by up to two R⁸¹ radicals,

R⁸¹ denotes OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro or NH₂, and

R⁹ denotes hydrogen, C₁-C₆-alkyl, C₁-C₄-alkylphenyl, CO₂-C₁-C₄-alkylphenyl, CO₂-C₁-C₄-alkyl, SO₂-phenyl, COR⁸ or phenyl, where the phenyl rings can be additionally substituted by up to two R⁹¹ radicals,

R⁹¹ denotes OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro or NH₂,

and also their tautomeric forms and possible enantiomeric and diastereomeric forms and their prodrugs.

2. Compounds of the formula I according to claim 1, in which

A denotes a benzo ring,

X¹ denotes O, and

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R¹ denotes hydrogen.

3. Compounds of the formula I according to claim 1, in which

B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R⁴ or at most 2 R⁵.

4. Compounds of the formula I according to claim 1, in which

L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R⁴ radicals and at most two different or identical R⁵ radicals,

v denotes 1, and

w denotes 0 or 1.

5. Compounds of the formula I according to claim 1, in which

R⁴ denotes D_{0,1}-F_{0,1}¹-G²-G³, where G³ denotes hydrogen,

D denotes O or NR⁴³, where R⁴³ denotes hydrogen or C₁-C₃-alkyl, and

F¹ denotes C₂-C₄-alkyl.

6. Compounds of the formula I according to claim 1, in which

R⁴ denotes G¹-F₀¹-G²-G³, where G³ denotes hydrogen, and

F¹ denotes C₁-C₂-alkyl.

7. Compounds of the formula I according to claim 6, in which

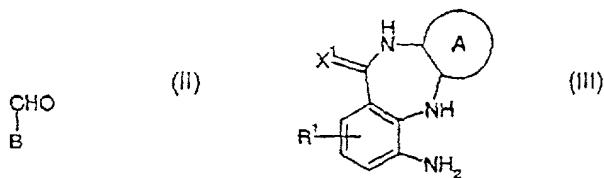
G¹ denotes imidazole or pyrrole, where the pyrrole can in each case be

substituted by at most three different or identical R⁵ radicals, and

F¹ denotes C₁-C₂-alkyl.

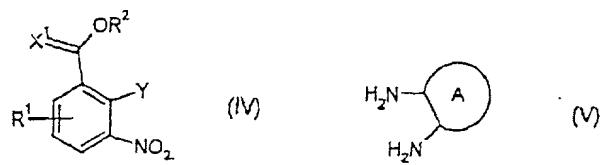
8. Pharmaceutical composition which comprises at least one compound according to claim 1 and also at least one customary carrier and/or auxiliary substance.
9. Use of a compound of formula I according to claim 1 for producing a pharmaceutical for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections.
10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at least one compound of the formula I according to claim 1.

11. Process for producing a compound according to claim 1, which comprises condensing an aldehyde of the formula II with a diamine of the formula III:



where the symbols in the formulae II and III have the same meaning as in claim 1.

12. Process according to claim 11, where the diamine of the formula III is obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



where the symbols in the formulae IV and V have the same meaning as in Claim 1 and R^2 denotes branched or unbranched, saturated or unsaturated $\text{C}_1\text{-C}_6$ -alkyl.